FORM PTO-1390 (Modified) (REV 11-2000) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER	U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR
208858US0PCT	09/831888

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP99/09002	23 November 1999	25 November 1998 (earliest)

TITLE OF INVENTION
PRESSURISED METERED DOSE INHALERS (MDI)

APPLICANT(S) FOR DO/EO/US
LEWIS David et al.

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include itens (5), (6), (9) and (24) indicated below.
4. ☒ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
   a. ☐ is attached hereto (required only if not communicated by the International Bureau).
   b. ☒ has been communicated by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. ☐ is attached hereto.
   b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. ☐ are attached hereto (required only if not communicated by the International Bureau).
   b. ☐ have been communicated by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
10. ☐ An English language translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).
11. ☒ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☒ A copy of the International Search Report (PCT/ISA/210).

Items 13 to 20 below concern document(s) or information included:

13. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☐ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
20. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
21. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
22. ☐ Certificate of Mailing by Express Mail
23. ☒ Other items or information:

Notice for Consideration of Documents Cited in International Search Report
Notice of Priority

JC03 Rec'd PCT/PTO 23 MAY 2001

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
09/831888	PCT/EP99/09002	208858US0PCT

24. The following fees are submitted:.		CALCULATIONS PTO USE ONLY	
BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :			
☐ Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO	$1000.00		
☒ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO	$860.00		
☐ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO	$710.00		
☐ International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4)	$690.00		
☐ International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4)	$100.00		
ENTER APPROPRIATE BASIC FEE AMOUNT =		$860.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☒ 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).		$130.00	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	- 20 =	0	x $18.00	$0.00	
Independent claims	- 3 =	0	x $80.00	$0.00	
Multiple Dependent Claims **(check if applicable).**			☐	$0.00	
TOTAL OF ABOVE CALCULATIONS =				$990.00	
☐ Applicant claims small entity status. (See 37 CFR 1.27). The fees indicated above are reduced by 1/2.				$0.00	
SUBTOTAL =				$990.00	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (f)). +				$0.00	
TOTAL NATIONAL FEE =				$990.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) **(check if applicable).** ☐				$0.00	
TOTAL FEES ENCLOSED =				$990.00	
				Amount to be: refunded	$
				charged	$

a. ☒ A check in the amount of **$990.00** to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. _____ in the amount of _____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. **15-0030** A duplicate copy of this sheet is enclosed.

d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

22850

Surinder Sachar
Registration No. 34,423

Surinder Sachar

SIGNATURE

Norman F. Oblon

NAME

24,618

REGISTRATION NUMBER

May 23 2001

DATE

208858US-0 PCT

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF: :

DAVID LEWIS ET AL : ATTN: APPLICATION DIVISION

SERIAL NO: 09/831,888 :

FILED: MAY 23, 2001 :

FOR: PRESSURISED METERED DOSE INHALERS (MDI)

PRELIMINARY AMENDMENT

ASSISTANT COMMISSIONER FOR PATENTS
WASHINGTON, D.C. 20231

SIR:

Prior to examination on the merits, please amend the above-identified application as follows.

IN THE CLAIMS

Please amend the claims as shown on the marked-up copy following this amendment to read as follows:

4. (Amended) Pressurized metered dose inhalers according to claim 1, containing a low-volatility component selected from glycerol, polyethylene glycol and isopropyl myristate.

5. (Amended) Pressurized metered dose inhalers according to claim 1, wherein the co-solvent is ethanol.

6. (Amended) Pressurized metered dose inhalers according to claim 1, wherein the propellant is selected from HFA 227, HFA 134a and their mixtures.

7. (Amended) Pressurised metered dose inhalers according to claim 1, wherein part or all of the internal surfaces are coated with an epoxy phenol resin.

8. (Amended) Pressurised metered dose inhalers according to claim 1, wherein part or all of the internal surfaces consist of anodised aluminium.

9. (Amended) Stabilized aerosol solution formulation consisting of an active ingredient in a hydrofluorocarbon propellant, a co-solvent and optionally a low-volatility component for use in a pressurised metered dose inhaler as claimed in claim 1.

REMARKS

Claims 1-10 are active in the present application. Claims 4-9 have been amended to remove multiple dependencies. No new matter is added. An action on the merits and allowance of claims is solicited.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.

Norman F. Oblon
Attorney of Record
Registration No. 24,618

Daniel J. Pereira, Ph.D.
Registration No. 45,518

22850

(703) 413-3000
Fax #: (703)413-2220
NFO/DJPER/SUKOS/js

I:\atty\SUKOS\June\208858US-PR.wpd

Marked-Up Copy
Serial No: 09/831,888
Amendment Filed on:
07-19-01

IN THE CLAIMS

--4. (Amended) Pressurized metered dose inhalers according to [any of claims from 1 to 3] claim 1, containing a low-volatility component selected from glycerol, polyethylene glycol and isopropyl myristate.

5. (Amended) Pressurized metered dose inhalers according to [any of claims from 1 to 4] claim 1, wherein the co-solvent is ethanol.

6. (Amended) Pressurized metered dose inhalers according to [any of claims from 1 to 5] claim 1, wherein the propellant is selected from HFA 227, HFA 134a and their mixtures.

7. (Amended) Pressurised metered dose inhalers according to [any of claims 1 to 6] claim 1, wherein part or all of the internal surfaces are coated with an epoxy phenol resin.

8. (Amended) Pressurised metered dose inhalers according to [any of claims 1 to 5] claim 1, wherein part or all of the internal surfaces consist of anodised aluminium.

9. (Amended) Stabilized aerosol solution formulation consisting of an active ingredient in a hydrofluorocarbon propellant, a co-solvent and optionally a low-volatility component for use in a pressurised metered dose inhaler as claimed in [any of claims 1 to 8] claim 1.--

"PRESSURISED METERED DOSE INHALERS (MDI)"

The invention relates to the use of pressurised metered dose inhalers (MDIs) having part or all of their internal surfaces consisting of stainless steel, anodised aluminium or lined with an inert organic coating. The invention also relates to compositions to be delivered with said MDIs.

Pressurised metered dose inhalers are well known devices for administering pharmaceutical products to the respiratory tract by inhalation.

Active materials commonly delivered by inhalation include bronchodilators such as ß2 agonists and anticholinergics, corticosteroids, anti-leukotrienes, anti-allergics and other materials that may be efficiently administered by inhalation, thus increasing the therapeutic index and reducing side effects of the active material.

MDI uses a propellant to expel droplets containing the pharmaceutical product to the respiratory tract as an aerosol.

For many years the preferred propellants used in aerosols for pharmaceutical use have been a group of chlorofluorocarbons which are commonly called Freons or CFCs, such as CCl_3F (Freon 11 or CFC-11), CCl_2F_2 (Freon 12 or CFC-12), and $CClF_2$-$CClF_2$ (Freon 114 or CFC-114).

Recently, the chlorofluorocarbon (CFC) propellants such as Freon 11 and Freon 12 have been implicated in

the destruction of the ozone layer and their production is being phased out.

Hydrofluoroalkanes [(HFAs) known also as hydro-fluoro-carbons (HFCs)] contain no chlorine and are considered less destructive to ozone and these are proposed as substitutes for CFCs.

HFAs and in particular 1,1,1,2-tetrafluoroethane (HFA 134a) and 1,1,1,2,3,3,3-heptafluoropropane (HFA 227) have been acknowledged to be the best candidates for non-CFC propellants and a number of medicinal aerosol formulations using such HFA propellant systems have been disclosed.

Many of these applications, in which HFAs are used as propellant, propose the addition of one or more of adjuvants including compounds acting as co-solvents, surface active agents including fluorinated and non-fluorinated surfactants, dispersing agents including alkylpolyethoxylates and stabilizers.

In the international application n°PCT/EP98/03533 filed on 10/06/98 the applicant described solution compositions for use in an aerosol inhaler, comprising an active material, a propellant containing a hydrofluoroalkane (HFA), a cosolvent and further comprising a low volatility component to increase the mass median aerodynamic diameter (MMAD) of the aerosol particles on actuation of the inhaler.

Compositions for aerosol administration via MDIs can be solutions or suspensions. Solution compositions offer several advantages: they are convenient to

manufacture being completely dissolved in the propellant vehicle and obviate physical stability problems associated with suspension compositions.

The widespread use of these formulations is limited by their chemical instability, causing the formation of degradation products.

WO94/13262 proposes the use of acids as stabilisers preventing the chemical degradation of the active ingredient in aerosol solution formulations comprising HFAs. Among the selected medicaments ipratropium bromide is comprised, for which many composition examples are supplied, in which the active ingredient is in combination with an organic or inorganic acid.

WO96/32099, WO96/32150, WO96/32151 and WO96/32345 disclose metered dose inhalers for the administration of different active ingredients in suspension in the propellant, wherein the internal surfaces of the inhaler are partially or completely coated with one or more fluorocarbon polymers optionally in combination with one or more non-fluorocarbon polymers.

Said applications do not however address the technical problem of the chemical stability of the active ingredient but they rather concern a different problem, namely that of the adhesion of micronized particles of the suspended active ingredient to the internal surfaces of the inhaler, such as the can walls, valves and sealings. It is also known from Eur. J. Pharm. Biopharm. 1997, 44, 195 that suspensions of

drugs in HFA propellant are frequently subjected to absorption of the drug particles on the valves and on the internal walls of the inhaler. The properties of an epoxy phenol resin coating of the aerosol cans have been studied to circumvent this problem.

WO 95/17195 describes aerosol compositions comprising flunisolide, ethanol and HFA propellants. It is stated in the document that conventional aerosol canisters can be used to contain the composition and that certain containers enhance its chemical and physical stability. It is suggested that the composition can be preferably contained in vials coated with resins such as epoxy resins (e.g. epoxy-phenolic resins and epoxy-urea-formaldehyde resins).

Actually the results reported in Tables 5, 6 and 8 respectively on pages 16 and 19 of the cited application demonstrate that flunisolide decomposes only in plastic cans (Table 8), and that the percent drug recovery in compositions stored in aluminium, glass or epoxy-phenol formaldehyde resin coated vials is practically the same (Table 8). In other words there is no difference between aluminium, glass type III or epoxy/phenol-formaldehyde resin coated aluminium vials coated by Cebal. No data are reported for other types of epoxy resins.

It has now been found that the chemical stability problems of active ingredients in solution in HFA propellants can be eliminated by storing and delivering said composition employing metered-dose

inhalers having part or all of their internal metallic surfaces consisting of stainless steel, anodised aluminium or lined with an inert organic coating.

The preferred material for the aerosol cans is anodised aluminium.

In the case of epoxy-phenol resin coating the choice of the suitable coating will be opportunely made on the basis of the characteristics of the active ingredient.

The most widely used epoxy resins in can coatings are produced by the reaction of epichlorohydrin and bisphenol A (DGEBPA). Variations in the molecular weight and in the polymerisation degree result in resins of different properties.

Phenoxy resins are other commercially important thermoplastic polymers derived from bisphenols and epichlorohydrin, characterized in that their molecular weights (MWs) are higher, ie, ca 45000, than those of conventional epoxy resins, ie, 8000 and lack terminal epoxide functionality.

Other multifunctional resins are epoxy-phenol-novolac and epoxy-cresol-novolac resins obtained by glycidylation of the phenol-formaldehyde (novolac) or of the o-cresol-formaldehyde (o-cresol novolac) condensates respectively.

The inhalers according to the invention effectively prevent the chemical degradation of the active ingredient.

Surprisingly and contrary to what reported in the

prior art with regard to flunisolide, we found a considerable degradation of the tested active ingredients when their formulations were stored in glass containers type III.

Summary of the invention

Pressurised metered dose inhalers for dispensing solution of an active ingredient in a hydrofluorocarbon propellant, a co-solvent and optionally a low-volatility component characterized in that part or all of the internal surfaces of said inhalers consist of stainless steel, anodised aluminium or are lined with an inert organic coating.

Detailed description of the invention

Pressurised metered dose inhalers are known devices, usually consisting of a main body or can, acting as a reservoir for the aerosol formulation, a cap sealing the main body and a metering valve fitted in the cap.

MDIs are usually made of a conventional material such as aluminium, tin plate, glass, plastic and the like.

According to the invention, part or all of the internal surfaces of the inhalers consists of stainless steel, anodised aluminium or is lined with an inert organic coating. One of the preferred coating consists of epoxy-phenol resin. Any kind of stainless steel may be used. Suitable epoxy-phenol resins are commercially available.

Active ingredients which may be used in the

aerosol compositions to be dispensed with the inhalers of the invention are any ingredient which can be administered by inhalation and which meets problems of chemical stability in solution in HFA propellants giving rise to a decomposition when stored in conventional materials cans and in particular in aluminium cans.

In the compositions to be delivered with the MDIs of the invention the hydrofluorocarbon propellant is preferably selected from the group of HFA 134a, HFA 227 and mixtures thereof.

The co-solvent is usually an alcohol, preferably ethanol. The low volatility component, when present, is selected from the group of glycols, particularly propylene glycol, polyethylene glycol and glycerol, alkanols such as decanol (decyl alcohol), sugar alcohols including sorbitol, mannitol, lactitol and maltitol, glycofural (tetrahydro-furfurylalcohol) and dipropylene glycol, vegetable oils, organic acids for example saturated carboxylic acids including lauric acid, myristic acid and stearic acid; unsaturated carboxylic acids including sorbic acid, and especially oleic acid; saccharine, ascorbic acid, cyclamic acid, amino acids, or aspartame, esters for example ascorbyl palmitate, isopropyl myristate and tocopherol esters; alkanes for example dodecane and octadecane; terpenes for example menthol, eucalyptol, limonene; sugars for example lactose, glucose, sucrose; polysaccharides for example ethyl cellulose, dextran; antioxidants for

example butylated hydroxytoluene, butylated hydroxyanisole; polymeric materials for example polyvinyl alcohol, polyvinyl acetate, polyvinyl pyrrolidone; amines for example ethanolamine, diethanolamine, triethanolamine; steroids for example cholesterol, cholesterol esters. The low-volatility component has a vapour pressure at 25°C lower than 0.1 kPa, preferably lower than 0.05 kPa.

The aerosols compositions to be delivered with the pressurised MDIs of the invention may contain from 0.2 to 2% by weight of said low volatility component.

Propylene glycol, polyethylene glycol, isopropyl myristate and glycerol are particularly preferred low-volatility components.

The function of the low volatility component is to modulate the MMAD of the aerosol particles. Being used at very low concentrations, it does not substantially affect the chemical stability of the compositions.

Examples of active ingredients include: anticholinergics such as ipratropium bromide, oxitropium bromide, tiotropium bromide; acetal corticosteroids such as budesonide, ciclesonide, rofleponide; chetal corticosteroids such as flunisolide, triamcinolone acetonide; other corticosteroids such as fluticasone propionate, mometasone furoate; short or long acting beta-adrenergic agonists such as salbutamol, formoterol, salmeterol, TA 2005 and their combinations. The active ingredients when possible may be present in racemic

mixtures or in form of a single enantiomer or epimer.

As said before, WO 94/13262 teaches that problems of chemical stability of medicaments and in particular of ipratropium bromide in aerosol solution compositions can be solved adding an acid, either an inorganic acid or an organic acid, to the HFA propellant/cosolvent system.

Examples of compositions containing ipratropium bromide in HFA 134a/ethanol systems further containing an inorganic acid such as hydrochloric, nitric, phosphoric or sulfuric acid or an organic acid such as ascorbic or citric acid are provided.

We found that in solution compositions comprising ipratropium bromide, a propellant containing a hydrofluoroalkane, a cosolvent and further comprising a low volatility component:

a) different decomposition rates occur with different acids: for example we found that ipratropium bromide (20 μg/dose) in a composition of 13% (w/w) ethanol, 1.0% (w/w) glycerol, 20 μl/can of 1N hydrochloric acid and HFA 134a to 12 ml/can rapidly decomposes and after 3 months storage at 40°C gives 85.0 % average of drug remaining;

b) ipratropium bromide with or without acids is stable in stainless steel, anodised aluminium or in some types of epoxy phenol resin lined cans;

c) surprisingly certain kinds of materials, such as glass, coatings proposed in the prior-art to overcome the physical absorption phenomenon of the

active ingredient, such as perfluoroalkoxyalkanes and fluorinated-ethylene-propylene polyether sulfone resins, or certain kinds of epoxy phenol coatings turned out to be completely unsatisfactory and ineffective in preventing its chemical degradation.

Another preferred active ingredient for the preparation of solution compositions in a HFA/cosolvent system to be dispensed by MDIs according to the present invention is budesonide.

Previously HFA/budesonide compositions have been described, in which budesonide is present in suspension in the propellant system and the composition further comprises additional ingredients such as particular kinds of surfactants (EP 504112, WO 93/05765, WO 93/18746, WO 94/21229).

In WO 98/13031 it is reported that suspension formulations of budesonide have a propensity to rapidly form coarse flocs upon dispersion and redispersion which may deleteriously affect dosage reproducibility. There is also a tendency for budesonide to deposit from suspension onto the walls of the container.

To achieve stable suspensions of particulate budesonide it is employed in the prior art a composition containing a mixture of HFA propellants to match the density of the propellant mixture to be substantially identical to the density of budesonide, up to 3% of an adjuvant such as ethanol and small amounts of surfactant.

It is stated in the document that the levels of the adjuvants are low to avoid significant solubilization of drug, leading to a problem of chemical degradation and particle size increase on storage.

In the solution compositions of the present invention budesonide is chemically and physically stable.

The aerosol compositions of the invention distributed in inhalers having the internal surfaces consisting of stainless steel, anodised aluminium or coated with an inert material and preferably with epoxy-phenol resin are stable for long periods and do not undergo chemical degradation.

Also in this case a considerable degradation of the active ingredient was noticed when glass containers were used.

Analogously flunisolide and dexbudesonide (the 22R-epimer of budesonide) solutions in HFA propellant containing ethanol and a low-volatility component are stable when stored in inhalers having the internal surfaces consisting of anodised aluminium or coated with epoxy-phenol resin. Evident degradation of flunisolide was noticed when glass containers were used.

It has been also found that the low volatility component may also act as a co-solvent, thus increasing the solubility of the drug in the formulation and increasing the physical stability

and/or allowing the possibility to decrease the quantity of co-solvent required.

The following examples further illustrate the invention. In the examples and tables the different types of epoxy phenol resins are indicated with numbers in brackets corresponding to:

(1) Epoxy-phenol lacquered aluminium vials coated by Cebal

(2) Epoxy-phenol lacquered aluminium vials coated by Presspart

(3) Epoxy-phenol lacquered aluminium vials coated by Nussbaum & Guhl

(4) Epoxy-phenol lacquered aluminium vials coated by Presspart, other than (2)

Example 1

A composition containing 4.8 mg of ipratropium bromide (20 μg/dose), 13% (w/w) ethanol, 1.0% (w/w) glycerol and HFA 134a to 12 ml/can was distributed in stainless steel, anodised aluminium, standard aluminium cans or in cans having different internal coatings and were stored at various conditions.

The results are reported in Table 1 and Table 2.

The percent drug remaining in the composition, measured by HPLC, shows that stainless steel and anodised aluminium cans as well as epoxy-phenol resins (1), (2) and (4) coated cans are effective in preventing the chemical degradation of ipratropium bromide, differently from glass cans or other tested coatings.

Example 2

The effect of different acids on the chemical stability of the composition of Example 1 was studied.

Citric, ascorbic and hydrochloric acids were added to the formulations in the amounts reported in Table 3.

The stability of the compositions was tested after 1, 2 and 5 months storage at 40°C in epoxy-phenol resin (4) coated cans.

Example 3

Compositions containing 12 mg of budesonide (50 μg/dose), 13% or 15% (w/w) ethanol, 1.3% (w/w) glycerol in HFA 134a to 12 ml/can were distributed in stainless steel, anodised aluminium, standard aluminium, glass cans or in cans having different internal coatings and were stored at various conditions.

The results are reported in Table 4 and 5.

The percent drug remaining in the compositions, measured by HPLC, shows the favourable effect of stainless steel, anodised aluminium and inert coating on the chemical stability of the active ingredient in respect to standard aluminium or glass cans. The best results have been obtained with stainless steel, anodised aluminium cans and with epoxy-phenol or perfluoroalkoxyalkane coatings.

Example 4

A composition containing 48 mg of dexbudesonide (200 μg/dose), 15% (w/w) ethanol, 1.3% (w/w) glycerol

in HFA 134a to 12 ml can was distributed in epoxy-phenol lacquered aluminium cans and was stored at 40°C.

The percent drug remaining in the composition after 8 months, measured by HPLC, was 95.4 % (average value referred to two tests).

The control of the epimeric distribution showed that there is no transfer from the 22R to the 22S epimer.

Example 5

Compositions containing 7.2, 12, 16.8 mg of dexbudesonide (corresponding to 30, 50 and 70 µg/dose respectively), ethanol, 0.9 (w/w) PEG 400 or isopropyl myristate (IPM) in HFA 227 to 12 ml can was distributed in aluminium anodised cans and was stored 70 days at 50°C. The results are reported in Table 6.

The percent drug remaining in the composition measured by HPLC shows the favourable effect of anodised aluminium cans on the chemical stability of the active ingredient. The control of the epimeric distribution showed that there is no transfer from the 22R to the 22S epimer.

Example 6

The fine particle dose (FPD: weight of particles having an aerodynamic diameter lower than 4.7 µm) of dexbudesonide solution compositions in HFA 134a or HFA 227, prepared following the examples 4 and 5, was determined.

The experiments were performed using the Andersen

Cascade Impactor and the data obtained are average values from 10 shots.

The results, reported in Table 7 and 8 show that dexbudesonide formulations of the invention are characterized by a very low dose and a very high fine particle dose.

The FPD gives a direct measure of the mass of particles within the specified size range and is closely related to the efficacy of the product.

Example 7

A composition containing 60 mg of flunisolide (250 µg/dose), 15% (w/w) ethanol, 1% (w/w) glycerol in HFA 134a to 12 ml/can was distributed in anodised aluminium, glass cans or in cans having different internal coatings and were stored for 41 days at 50° C.

The results are reported in Table 9.

The percent drug remaining in the composition, measured by HPLC, shows the favourable effect of anodised aluminium and inert coating with epoxy-phenol resins on the chemical stability of the active ingredient in respect to glass cans.

Example 8

The solubility of ipratropium bromide and micronized budesonide in ethanol, glycerol and their mixtures has been investigated.

The tests were carried out at room temperature.

a) Solubility in ethanol.

About 8.5 g of absolute ethanol were weighed into

a flask. The active ingredient (Ipratropium Bromide or Budesonide) was added in small amounts, under magnetic stirrer, until no further dissolution occurred (i.e.: a saturated solution was obtained). The flask was stirred for about 40 minutes, and left to settle overnight prior to analysis, to let the system equilibrate. The flask was kept sealed, to avoid evaporation.

The solution obtained was then filtered and tested for the amount of active ingredient, according to the conventional analytical procedure.

b) Solubility in ethanol/glycerol mixtures.

The required amounts of ethanol and glycerol were weighted into a flask, and mixed by a magnetic stirrer until a homogeneous phase was obtained.

The solubility of ipratropium bromide in ethanol is 42.48 mg/g.

The solubility data of ipratropium bromide in ethanol/glycerol mixtures are listed in Table 10.

The solubility of micronized budesonide in ethanol is 31.756 mg/g.

Solubility data of micronized budesonide in ethanol/glycerol mixtures are listed in Table 11.

The data show that both the tested active ingredients are rather soluble in ethanol, and that their solubility increases even when small percentages of glycerol are added.

The increase in solubility is maintained also in presence of HFA propellants.

TABLE 1: Percent ipratropium bromide (IPBr) recovered after storing the composition of Example 1 for 8 months at 40°C in cans of different types

CAN TYPE	% RESIDUAL IPBr
Epoxy-phenol resin (4)	96
Perfluoroalkoxyalkane	57
Fluorinated-ethylene-propylene/ polyether sulphone (Xylan 8840(R))	78
Stainless steel	96
Standard aluminium	46

TABLE 2: Percent ipratropium bromide (IPBr) recovered after storing the composition of Example 1 for 30 and 60 days at 50°C, or for 96 days at 40°C in cans of different types (average values referred to two tests).

CAN TYPE	% RESIDUAL IPBr (% RESIDUAL IPBr RELATIVE TO t=0)			
	t=0	t=30 days at 50°C	t=60 days at 50°C	t=96 days at 40°C
Epoxy phenol resin (1)	99	89 (90)	88.5 (89.5)	93.5 (94.5)
Epoxy phenol resin (2)	97.5	90 (92)	88.5 (90.5)	89 (91)
Epoxy phenol resin (3)	98.5	56.5 (57.5)	46 (47)	52.5 (53.5)
Anodised aluminum	94	89 (95)	87 (92.5)	90.5 (96.5)
Glass type III *	-	48.5 (-)	41.5 (-)	47 (-)

* according to Eur Pharmacopoeia 3rd Ed Suppl 1999

TABLE 3: Percent ipratropium bromide (IPBr) recovered after storing the compositions of Example 1, with different acids added, in epoxy-phenol (4) coated cans (average values referred to two tests)

Acid	% RESIDUAL IPBr (% RESIDUAL IPBr RELATIVE TO t=0)			
	t=0	t=1 month at 40°C	t=2 months at 40°C	t=5 months at 40°C
Citric (0.6% w/w)	98	98 (100)	99 (101)	94 (96)
(0.3% w/w)	99	99 (100)	100 (101)	97 (98)
(0.07% w/w)	99	98 (99)	99 (100)	96 (97)
Ascorbic	119	113 (95)	112 (94)	110 (92)
Hydrochloric (4µl-1N)	101	100 (99)	104 (102)	96 (95)
(10 µl-1N)	101	98 (97)	98 (97)	97 (96)
(20 µl-1N)	100	95 (95)	98 (98)	97 (97)
None	97	97 (100)	98 (101)	95 (98)

TABLE 4: Percent budesonide recovered after storing the composition of Example 3 (13% ethanol) for 7 months at 40°C in cans of different types

CAN TYPE	% RESIDUAL BUDESONIDE
Epoxy-phenol resin (4)	100
Fluorinated-ethylene-propylene/ polyether sulphone (Xylan 8840(R))	93.5
Stainless steel	97
Aluminium	68
Perfluoroalkoxyalkane	100

TABLE 5: Percent budesonide recovered after storing the composition of Example 3 (15% ethanol) for 33 and 73 days at 50°C in cans of different types (average values referred to two tests).

CAN TYPE	% RESIDUAL BUDESONIDE (% RESIDUAL BUDESONIDE RELATIVE TO t= 0)		
	t=0	T=33 days	t=73 days
Epoxy phenol resin (1)	99.3	97.0 (97.7)	95.4 (96.1)
Epoxy phenol resin (2)	99.5	96.6 (97.0)	95.6 (96.1)
Epoxy phenol resin (3)	99.3	96.6 (97.2)	95.9 (96.5)
Anodised aluminium	99.9	99.2 (99.3)	97.7 (97.8)
Glass type III *	-	86.15 (-)	80.4 (-)

* according to Eur Pharmacopoeia 3rd Ed Suppl 1999

These results have been confirmed storing the same formulation up to 7 months at 30°C, 40°C, 45°C and 50°C.

TABLE 6: Percent dexbudesonide recovered after storing the compositions of Example 5 for 70 days at 50°C in anodised aluminium cans (average values referred to two tests).

Metered dose (µg)	Ethanol % (w/w)	Low vol.comp. 0.9% (w/w)	% Residual dexbudesonide (% residual dexbudesonide relative to t =0)	
			t = 0 days	t = 70 days
30	5	PEG 400	95.8	95.8 (100)
		IPM	98.1	96.8 (98.7)
50	8	PEG 400	99.0	98.0 (98.9)
		IPM	98.0	99.4 (101)
70	7	PEG 400	95.7	93.75 (98.0)
		IPM	100.4	96.3 (96.0)

IPM = Isopropyl myristate

TABLE 7: Fine particle dose (FPD) values of dexbudesonide solution formulation in HFA 134a containing:

dexbudesonide 14.4 mg/can (60 µg/shot)

ethanol 8 % (w/w)

low volatility compound 0.9% (w/w)

HFA 134a to 12 ml can (valve chamber volume = 63 µl)

MMAD = 2.0 µm

Low volatility Compound	FPD (µg)	FPF (%)	Metered dose (µg)	Delivered dose (µg)
IPM	39.9	73.6	57.9	54.2
IPM	39.4	77.4	53.2	50.9

IPM = isopropyl myristate

FPF = fine particle fraction (Fine particle dose / Delivered dose x 100)

FPD = weight of particles having an aerodynamic diameter lower than 4.7 µm

Metered dose is given by the sum of delivered dose and actuator residue.

Delivered dose is the dose delivered ex actuator.

TABLE 8: Fine particle dose (FPD) values of dexbudesonide solution formulation in HFA 227 containing:
dexbudesonide 15.12 mg/can (63 µg/shot)
ethanol 7 % (w/w)
low volatility compound 0.9% (w/w)
HFA 227 to 12 ml can (valve chamber volume = 63 µl)
MMAD = 2.0 µm

Low volatility Compound	FPD (µg)	FPF (%)	Metered dose (µg)	Delivered dose (µg)
IPM	45.0	75.5	63.9	59.7
PEG 400	48.5	78.9	65.5	61.5

IPM = isopropyl myristate
FPF = fine particle fraction (Fine particle dose / Delivered dose x 100)
FPD = weight of particles having an aerodynamic diameter lower than 4.7 µm
Metered dose is given by the sum of delivered dose and actuator residue
Delivered dose is the dose delivered ex actuator

TABLE 9: Percent flunisolide recovered after storing the composition of Example 7 for 41 days at 50°C in cans of different types (average values referred to two tests).

CAN TYPE	% RESIDUAL FLUNISOLIDE (% RESIDUAL FLUNISOLIDE RELATIVE TO t=0))		
	t=0	t=41 days	t=93 days
Epoxy phenol resin (1)	98.4	99.2 (101)	101.4 (103)
Epoxy phenol resin (2)	101.9	99.7 (97.8)	101.9 (100)
Epoxy phenol resin (3)	101.7	99.2 (97.5)	101.2 (99.6)
Anodised aluminum	101.6	100.4 (98.8)	100.7 (99.1)
Glass type III *	-	-	97.5 (-)

* according to Eur Pharmacopoeia 3rd Ed Suppl 1999

TABLE 10: Solubility of Ipratropium Bromide in ethanol/glycerol mixtures

Ethanol (%)	Glycerol (%)	Ipratropium Bromide solubility (mg/g)
100	0	42.8
92.6	7.4	74.0
91.9	8.1	74.7
91.3	8.7	90.5
88.4	11.6	98.0
82.6	17.4	115.6
71.4	28.6	196.7
60	40	271.6
40	60	307.2
21.1	78.9	265.7
0	100	73.4

TABLE 11: Solubility of micronized Budesonide in ethanol/glycerol mixtures

Ethanol (%)	Glycerol (%)	Budesonide solubility (mg/g)
100	0	31.756
92.5	7.5	36.264
91.9	8.1	36.277
91.3	8.7	37.328
87.7	12.3	38.364
83.3	16.7	37.209
71.4	28.6	35.768
60	40	28.962
39.9	60.1	14.840
21.1	78.9	3.990
0	100	0.214

CLAIMS

1. Pressurised metered dose inhalers containing a solution of an active ingredient in a hydrofluorocarbon propellant, a co-solvent and optionally a low-volatility component characterised in that part or all of the internal surfaces of said inhalers consist of stainless steel, anodised aluminium or are lined with an inert organic coating selected from perfluoroalkoxyalkane, epoxy-phenol resin or fluorinated-ethylene-propylene polyether sulfone, said material preventing the chemical degradation of the active ingredient.

2. Pressurized metered dose inhalers according to claim 1, wherein the active ingredients are selected from ß2 agonists, steroids or anti-cholinergic agents and their combinations.

3. Pressurized metered dose inhalers according to claim 2, wherein the active ingredient is ipratropium bromide, oxitropium bromide, tiotropium bromide, flunisolide, triamcinolone acetonide, fluticasone propionate, mometasone furoate, budesonide, ciclesonide, rofleponide and epimers thereof.

4. Pressurized metered dose inhalers according to any of claims from 1 to 3, containing a low-volatility component selected from glycerol,

polyethylene glycol and isopropyl myristate.

5. Pressurized metered dose inhalers according to any of claims from 1 to 4, wherein the co-solvent is ethanol.

6. Pressurized metered dose inhalers according to any of claims from 1 to 5, wherein the propellant is selected from HFA 227, HFA 134a and their mixtures.

7. Pressurised metered dose inhalers according to any of claims 1 to 6 wherein part or all of the internal surfaces are coated with an epoxy phenol resin.

8. Pressurised metered dose inhalers according to any of claims 1 to 5 wherein part or all of the internal surfaces consist of anodised aluminium.

9. Stabilized aerosol solution formulation consisting of an active ingredient in a hydrofluorocarbon propellant, a co-solvent and optionally a low-volatility component for use in a pressurised metered dose inhaler as claimed in any of claims 1 to 8.

10. Aerosol solution formulation of dexbudesonide in a hydrofluorocarbon propellant and ethanol as a co-solvent, further comprising a low volatility compound selected from glycerol, isopropylmyristate and polyethylene glycol.

9253V

Declaration, Power Of Attorney and Petition

WE (I) the undersigned inventor(s), hereby declare(s) that:

My residence, post office address and citizenship are as stated below next to my name,

We (I) believe that we are (I am) the original, first, and joint (sole) inventor(s) of the subject matter which is claimed and for which a patent is sought on the invention entitled

Pressurised metered dose inhalers (MDI)

the specification of which

- ☐ is attached hereto.
- ☐ was filed on _____ as
  Application Serial No. _____
  and amended on _____.
- ☒ was filed as PCT international application
  Number PCT/EP99/09002
  on 23.11.1999,
  and was amended under PCT Article 19
  on _____ (if applicable).

We (I) hereby state that we (I) have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

We (I) acknowledge the duty to disclose information known to be material to the patentability of this application as defined in Section 1.56 of Title 37 Code of Federal Regulations.

We (I) hereby claim foreign priority benefits under 35 U.S.C. § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed. Prior Foreign Application(s)

Application No.	Country	Day/Month/Year	Priority Claimed
MI98A002559	Italy	25.11.1998	☒ Yes ☐ No
MI99A001712	Italy	30.07.1999	☒ Yes ☐ No
			☐ Yes ☐ No
			☐ Yes ☐ No

We (I) hereby claim the benefit under Title 35, United States Code, § 119(e) of any United States provisional application(s) listed below.

(Application Number) (Filing Date)

(Application Number) (Filing Date)

We (I) hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s), or § 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. § 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR § 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

Application Serial No.	Filing Date	Status (pending, patented, abandoned)

And we (I) hereby appoint: Norman F. Oblon, Reg. No. 24,618; Marvin J. Spivak, Reg. No. 24,913; C. Irvin McClelland, Reg. No. 21,124; Gregory J. Maier, Reg. No. 25,599; Arthur I. Neustadt, Reg. No. 24,854; Richard D. Kelly, Reg. No. 27,757; James D. Hamilton, Reg. No. 28,421; Eckhard H. Kuesters, Reg. No. 28,870; Robert T. Pous, Reg. No. 29,099; Charles L. Gholz, Reg. No. 26,395; Vincent J. Sunderdick, Reg. No. 29,004; William E. Beaumont, Reg. No. 30,996; Robert F. Gnuse, Reg. No. 27,295; Jean-Paul Lavalleye, Reg. No. 31,451; Stephen G. Baxter, Reg. No. 32,884; Robert W. Hahl, Reg. No. 33,893; Richard L. Treanor, Reg. No. 36,379; Steven P. Weihrouch, Reg. No. 32,829; John T. Goolkasian, Reg. No. 26,142; Richard L. Chinn, Reg. No. 34,305; Steven E. Lipman, Reg. No. 30,011; Carl E. Schlier, Reg. No. 34,426; James J. Kulbaski, Reg. No. 34,648; Richard A. Neifeld, Reg. No. 35,299; J. Derek Mason, Reg. No. 35,270; Surinder Sachar, Reg. No. 34,423; Christina M. Gadiano, Reg. No. 37,628; Jeffrey B. McIntyre, Reg. No. 36,867; Paul E. Rauch, Reg. No. 38,591; William T. Enos, Reg. No. 33,128; and Michael E. McCabe, Jr., Reg. No. 37,182; our (my) attorneys, with full powers of substitution and revocation, to prosecute this application and to transact all business in the Patent Office connected therewith; and we (I) hereby request that all correspondence regarding this application be sent to the firm of OBLON, SPIVAK, McCLELLAND, MAIER & NEUSTADT, P.C., whose Post Office Address is: Fourth Floor, 1755 Jefferson Davis Highway, Arlington, Virginia 22202.

We (I) declare that all statements made herein of our (my) own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

LEWIS David
NAME OF FIRST SOLE INVENTOR

Residence: Via Palermo, 26/A
PARMA, Italy ITX

Signature of Inventor

Citizen of: Italy

Post Office Address: same as above

03.07.2001
Date

2-00 GANDERTON David
NAME OF SECOND JOINT INVENTOR

Residence: Via Palermo, 26/A
PARMA, Italy I T X

Signature of Inventor

Citizen of: UK

Post Office Address: same as above

David Ganderton

03.07.2001
Date

3-00 MEAKIN Brian
NAME OF THIRD JOINT INVENTOR

Residence: Sussex Lodge
5, OAKLEY, CLAVERTON DOWN
BATH BA2 6DS GBX

Brian Meakin

Signature of Inventor BRIAN JOHN MEAKIN

Citizen of: UK

Post Office Address: As above.

Date 6.6.01

4-00 VENTURA Paolo
NAME OF FOURTH JOINT INVENTOR

Residence: Via Palermo, 26/A
PARMA, Italy I T X

Signature of Inventor

Citizen of: Italy

Post Office Address: same as above

03.07.2001
Date

5-00 BRAMBILLA Gaetano
NAME OF FIFTH JOINT INVENTOR

Residence: Via Palermo, 26/A
PARMA, Italy I T X

Signature of Inventor

Citizen of: Italy

Post Office Address: same as above

03.07.2001
Date

Inventor's Signature: [signature] Date: 03.07.2001

Inventor:

(first) Raffaella MI (last) GARZIA (citizenship) Italian

Residence: (city) Parma (state/country) Italy IT X

Post Office Address: Via Palermo, 26/A - PARMA, Italy

(Zip Code) 43100

Inventor's Signature: ________ Date: ________

Inventor:

(first) MI (last) (citizenship)

Residence: (city) (state/country)

Post Office Address:

(Zip Code)

Inventor's Signature: ________ Date: ________

Inventor:

(first) MI (last) (citizenship)

Residence: (city) (state/country)

Post Office Address:

(Zip Code)

Inventor's Signature: ________ Date: ________

Inventor:

(first) MI (last) (citizenship)

Residence: (city) (state/country)

Post Office Address:

(Zip Code)

Inventor's Signature: ________ Date: ________

Inventor:

(first) MI (last) (citizenship)

Residence: (city) (state/country)

Post Office Address:

(Zip Code)

Inventor's Signature: ________ Date: ________

Inventor:

(first) MI (last) (citizenship)

Residence: (city) (state/country)

Post Office Address:

(Zip Code)

Inventor's Signature: ________ Date: ________

Inventor:

(first) MI (last) (citizenship)

Residence: (city) (state/country)

Post Office Address:

(Zip Code)

Inventor's Signature: ________ Date: ________

Inventor:

(first) MI (last) (citizenship)

Residence: (city) (state/country)

Post Office Address:

(Zip Code)

Inventor's Signature: ________ Date: ________

Inventor:

(first) MI (last) (citizenship)

Residence: (city) (state/country)

Post Office Address:

(Zip Code)